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Inhibition of Hepatitis C entry: too soon to dismiss while many are still being denied treatment

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Recently in Gut, Xiao et al. detailed an extensive analysis of synergistic inhibition of HCV achieved in various in vitro and in vivo models systems when HCV entry inhibitors were combined with different direct acting antivirals (DAAs) and host-targeted antiviral (HTAs).¹ However, a follow-up commentary by Pawlotsky suggested that “there is no unmet clinical need” for the treatment of HCV that cannot be addressed by the HCV drugs currently approved or in late stage clinical development.² Here we comment on the original study and subsequent commentary.

Consistent with the Xiao et al. study, we have reported that blocking the HCV entry factor Neimann-Pick-C1-like-1 (NPC1L1) with the FDA-approved drug ezetimibe synergistically inhibits chronic HCV infection in vitro when combined with interferon³ and, as we present in Figure 1, with HCV DAAs that block intracellular viral production. Importantly, we also showed that the synergy achieved was dependent on not only blocking cell-free virus entry, but also blocking HCV cell-to-cell spread.³ While blocking some HCV entry factors potentially inhibits HCV cell-to-cell spread (e.g. NPC1L1 , CLDN1, SRB1, EGFR), blocking other HCV entry factors (e.g. Tfr1 and CD81) has a smaller effect and still allows for substantial cell-to-cell spread. Relevant to this, we demonstrated that unlike ezetimibe, when an HCV entry inhibitor targeting Tfr1 was combined with interferon no synergy was observed.³ Similarly, in the Xiao et al. study,¹ combinations with anti-CD81 were in most cases the least synergistic/effective and anti-CD81 was not included at all in the chronic infection inhibition experiments. This is consistent with our proposal that the key to achieving synergy between viral entry inhibitors and other antivirals depends on whether the “entry inhibitor” also efficiently blocks viral cell-to-cell spread and thus highlights viral cell-to-cell spread as a previously unrecognized, but critically important antiviral drug target.

While the Pawlotsky commentary is correct that the insights from our and the Xiao et al. studies have significant implications for the treatment of other viral infections, it seems premature to assume that these findings are too late to be of benefit to those chronically infected with HCV. Two points in particular are relevant. First, we know that escape occurs during HCV DAA treatment, but in clinical trials the majority of patients clear the infection nonetheless.^{2,4} However, as acknowledged by Pawlotsky, the extent of viral resistance that will be encountered in real-life less-compliant populations remains unknown. In this regard, HCV entry/spread inhibitors could be beneficial as they increase the kinetics of viral decline limiting the time available for escape and also prevent the spread and thus subsequent amplification of escape mutants that may arise. Another issue not yet addressed in this discussion is cost. Although new extremely effective antivirals have been and continue to be approved, the prohibitive cost of these treatments place them out of reach for the majority of HCV-infected individuals with the most recent AASLD guidelines advocating treatment of only the sickest patients.⁵ Yet, the synergy data we³ (Fig. 1) and Xiao et al.¹ present, reveal that inexpensive FDA-approved drugs, such as ezetimibe, that inhibit HCV entry/ spread may have potential as adjunctive therapy to shorten therapy duration or be used in a cocktail in place of a more expensive DAA to help reduce these restrictive costs.

Hence, we would argue that considering the current number of patients not being treated, it would be hasty to dismiss HCV entry/spread inhibitors as a viable clinical option especially when some inexpensive potential candidates are already FDA-approved and have proven safe for human use.

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Figure Legends

Figure 1. Synergy between HCV entry/spread inhibitor ezetimibe and direct-acting antivirals. Chronically HCV infected Huh7 cells were mock-treated (black) or treated with 30 μ M ezetimibe (EZE; grey). (A) Parallel cultures were treated with 1 μ M of the HCV polymerase inhibitor RG7128 alone (RG7128; light blue) or in combination 30 μ M ezetimibe (RG + EZE; dark blue) (B) Parallel cultures were treated with 200nM of the HCV protease inhibitor ITMN5537 alone (ITMN5537; light blue) or in combination 30 μ M ezetimibe (ITMN + EZE; dark blue). At 24, 48, and 72 hours post-treatment, intracellular RNA was extracted. HCV and cellular GAPDH RNA levels were quantified by RT-qPCR. HCV copies were normalized to cellular GAPDH and are expressed as average number of HCV copies/ μ g RNA in triplicate samples \pm std dev. Significant differences between the DAA treated samples and the DAA + EZE treatment are indicated (F-test * P <0.05, ** P <0.005).

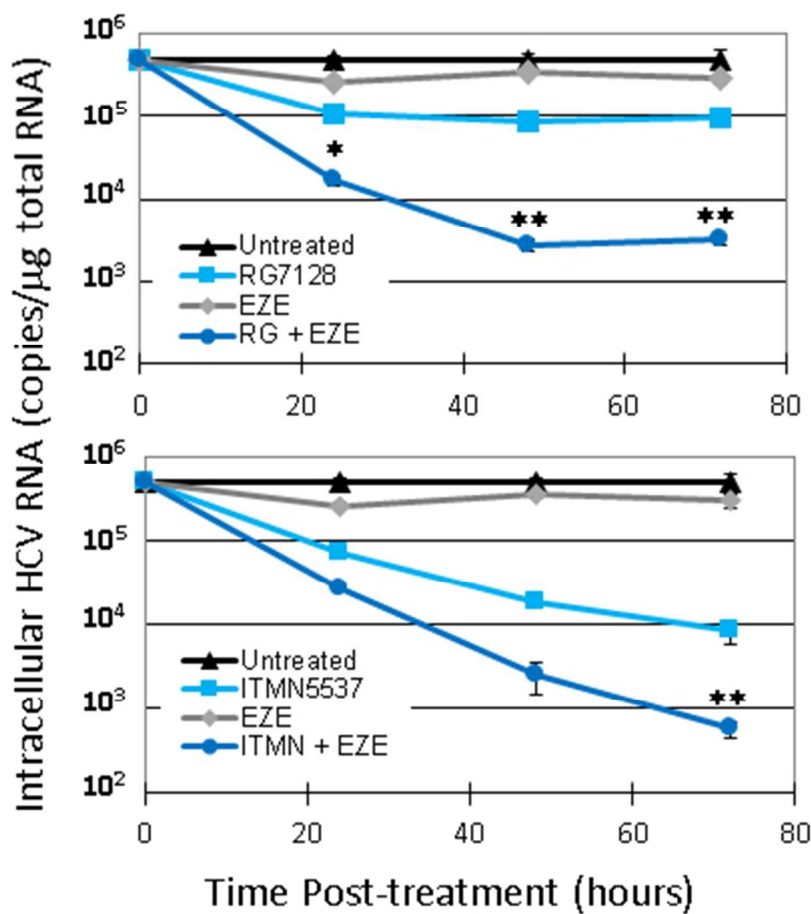


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